a yeast, mold or plant immunogen.

94. The kit of claim 59 wherein at least one immunogen is an insect immunogen.

95. The kit of claim 59 wherein at least one immunogen is an immunogen of an allogeneic or xenogeneic animal.

96. The kit of claim 61 wherein the labeling indicates that the kit, depending on when one or more of said immunogens is administered, can or does increase the incidence or accelerate the onset of said disorder.

97. The kit of claim 61 wherein the labeling indicates that the kit, depending on when one or more of said immunogens is administered, may, can or does increase the incidence of said disorder.

98. The kit of claim ~~59~~ 16 which includes at least one immunogen other than a pertussis immunogen.

99. The kit of claim ~~59~~ 16 which includes at least one immunogen other than a BCG immunogen.

100. The kit of claim ~~59~~ 16 where both (a) and (b) apply.

101. The method of claim 32 where at least one of said immunogens elicits an immune response in said mammal which recognizes an immunogen associated with an infectious disease to which said mammal is susceptible.--

REMARKS

Introductory Remarks

1.1. Both method and kit claims are presently pending. Applicant would be willing to cancel the method claims (without prejudice or disclaimer) if the Examiner would allow the "kit" claims.

1.2. Applicant requests a telephonic interview with the Examiner prior to the next action on this case. Applicant requests the participation of both the SPE and of Biotechnology Practice Specialist Richard Schwartz in that interview. It is

noted that Mr. Schwartz participated in an interview in a related case.

1.3. The double patenting rejection is improper as it relates to the "kit" claims, as they were restricted out in the parent case, see 35 USC §121. After all other issues are disposed of, Applicants will either (a) file a terminal disclaimer, or (b) cancel the method claims.

1.4. Our independent claims were method claims 31-33 and kit claims 25 and 27. We have added a new independent method claim (56) and replaced kit claim 25 with kit claim 59. Claims 2, 5, 6, 8, 9, 10, 14, 15, 16, 17, 21, 28, 29, 30, 48 and 50-54 were dependent on 31. However, claims 2, 9, 14, 17, 21, and 53 have been cancelled, and the other claims have been converted into kit claims dependent on 59 or 27. Independent claim 19 is to an immunogenic agent. Dependent claims 26, 34-41, 43, 44, 46, 49, 55 and 60-100 are also kit claims.

The rejection improperly indicates claims 3, 4, 7, 12, 13, 23 and 24 to be pending. They were cancelled during IPE.

Claim 32 has been amended to introduce the following limitations:

(1) if only one immunogen is administered, it is other than BCG;

(2) if the one immunogen is whole cell pertussis, the schedule is one other than a schedule of three doses at one week intervals, all given in the first month; and

(3) if all the immunogens administered are selected from a list of 10 immunogens, either

(a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is about two weeks,

or less.

Limitations (1) and (3) are copied from claim 1 of Classen, USP 5,728,385, which issued on the parent application, except that claim 32 refers to "one or more immunogens" instead of just "immunogens" to make it clear that a single immunogen could be administered. Note that the immunogens administered on different dates could be the same or different.

Limitation (2) is introduced to avoid any possibility of inherent anticipation by Adams (1947) (copy enclosed)[1], as cited in Table 5 of Halsey (of record). Excission of a prior art species from a generic claim is proper, see In re Johnson, 194 USPQ 187 (CCPA 1977) and indeed was contemplated as a possibility, see page 31, lines 9-18. The Halsey article is cited in the specification (p. 109) and incorporated by reference, as are all articles (including Adams) cited by Halsey. See pp. 99-100. Hence, there is no violation of the "description" requirement.

New claim 56 leaves out limitation (2) of claim 32, but instead requires that "one or more immunogens are administered on at least four different dates". This is supported by page 26, lines 4-6.

New claim 57 is supported by page 27, lines 9-12, and new claim 58, by page 27 lines 12-14 in conjunction with schedule 1 on page 107 (4 doses in first 42 days) and Example 2 (5 doses in first 42 days). A similar limitation was allowed in a dependent claim of the '385 patent.

New claim 59 as noted, replaces claim 25. It recites "protecting against an infectious disease", per page 54, lines 6-7, and page 68, instead of "reducing the incidence or severity of an infectious disease". By "protection", we mean, confers a beneficial clinical effect, see page 47, lines 7-10. Protection

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[1] Adams immunized with "phase I superconcentrate vaccine", with a total dose of "100,000,000,000 organisms".

is a matter of degree, see page 72, lines 15 and 21. The labeling limitations of old 25 have substantially became paragraph (a) of claim 59, while paragraph (b) relates to warnings regarding conventional immunizations and is based on pp. 53-69.

New claims 66-77 relate to the nature of the immunogen, and replace claims 17, 30, 42, 45, 47 and 53.

They are based as follows:

66= page 35, lines 20-24.

67= page 35, lines 24-26.

68= page 35, lines 20-21 and 26-28.

69= page 36, lines 1-10.

70= as for 67 and 69.

71= the Examples.

72 to 77= as for 66 to 71, respecively.

New claims 78-85 relate to the nature of the chronic immune-mediated disorder and are based on pages 21-22 of the specification.

New claims 86-89 are based on the disclosure at pages 69-76, and especially at page 70, lines 21-26 and page 75, lines 13-23.

New claim 90 is based on page 21, lines 9-10.

New claims 91-95 are based on page 34, lines 3-6.

1.5. We claim priority under §120 back to 08/104,529, filed June 25, 1993. This application is listed on the rule 1.63 declaration, so the OFR and the priority section of the action are in error.

2. Prior Art Issues

At the outset, we must point out that the Examiner improperly ignores the "use" language in the kit claims. While, in a claim to a product, language of intended use is ignored, these kit claims require the presence of certain labeling. This is a tangible requirement, not a mere statement of intended use.

The labeling is what the PTO calls "printed matter". Printed matter may constitute an element of a patentable claim and be given patentable weight, if there is a sufficient functional relationship between the printed matter and its substrate. See In re Gulack, 217 USPQ 401 (Fed. Cir. 1983); In re Miller, 164 USPQ 46 (CCPA 1969). Here, the printed matter explains how to use the substrate (the immunogen) to achieve the desired result.

The "printed matter" doctrine is closely allied with the old "mental steps" and later "mathematical algorithm" doctrines, and, in this regard, it is interesting to note that an invention applying the rules and instructions for a game ("Cricket") to an otherwise old dart machine was held to be potentially patentable because the algorithm was not a mathematical one. See Arachnid Inc. v. Medalist Mktg. Corp., 18 USPQ2d 1941 (W.D. Wash. 1991). The claimed instructions for use do not define a mathematical algorithm.

Gerbe, USP 3,627,122, SYSTEM AND APPARATUS FOR THE ADMINISTRATION OF DRUGS (1971), claims an apparatus comprising compartmented trays, with "a patient and dose identification card" covering the bottom of each compartment, the card "having a folded portion...for holding said card in place". The claim also recites that each compartment has "a longitudinal pocket in one wall for a signal identification card".

Phykitt, USP 5,687,841, COMBINATION SHIPPING CONTAINER, MIXING AND DRINKING VESSEL (1997) claims the combination of analgesic medications and a package which serves both a shipping container and a mixing vessel. Claims 21-22 recite

> 21. The combination, according to claim 1, wherein said package further includes at least one of indications, directions, warnings, drug interaction precautions, active ingredients information and storage information disposed on an outer surface of one of said back portion and said front

portion of said package.

22. The combination, according to claim 21, wherein said package includes each of said indications, said directions, said warnings, said drug interaction precautions, said active ingredients information and said storage information disposed on said outer portion of said back portion of said package.

Robertson, USP 5,752,723, PHARMACY LABEL AND PRESCRIPTION DRUG DISPENSING (1988) claims (18) "a labeled prescription drug package comprising...indicia comprising the name of a prescription drug, the dosage for proper administration of the drug, and the quantity of the drug to be provided in a package, imaged on said first label section".

See also Olney, USP 5,011,853 (claim 18= "a label which indicates that said pharmaceutical agent can be used for reducing the neurotoxicity of at least one cholinergic neurotoxin"); Kelly, USP 5,208,031 (claim 4= "the packaging material indicates that the sexual lubricant mixture... can reduce the risk of being infected by at least one type of sexually transmitted virus"); Sanders USP 4,820,635 (claim 1= "A kit ...comprising... instructions for performing the assay").

The purpose of the patent system is to encourage innovation. The claims are a means of defining the invention in such a manner that it is reasonably clear what has been patented. It is one thing to reject a claim because it covers subject matter which is disclosed or suggested by the prior art, or which is not enabled. It is quite another to reject it on what amounts to stylistic grounds.

The PTO and the courts have recognized the propriety of once exotic claim formats-- "Jepson" claims, "Markush" claims, "product-by-process" claims, "fingerprint" claims, and claims with "negative", "functional", or "alternative' limitations -- because they have realized that public policy demands that

inventors not be hindered by hypertechnical claim drafting rules from fully protecting novel, nonobvious, and adequately disclosed inventions.

The instant "kit" claims are a case in point. Applicant has discovered that immunization can --depending on timing - either increase or decrease the incidence or severity of chronic immune-mediated disorders such as diabetes and SLE. A traditional product claim does not sufficiently protect applicant, as it cannot cover a prior art vaccine, even if that vaccine were used without consideration of its effect on a chronic immune-mediated disorder.

For a method claim to protect the invention, it must be crafted to avoid any instance in which the prior art use of a vaccine to immunize against an infectious disease might inherently (although inadvertently) have had the effect of also reducing the incidence or severity of a chronic immune-mediated disorder, as otherwise it could be held invalid on the ground of "inherent anticipation". Applicant has studied the literature, and has attempted to phrase the claim so as to avoid inherent anticipation, but simply cannot be sure that all such art has been avoided. An early immunization protocol might be set forth in an old or obscure journal anywhere in the world, or might have been used "publicly", without formal publication, in the United States. Indeed, the specification at page 31, lines 9-18 expressly recognizes the problem:

> The inventor appreciates that it is conceivable that a prior experimenter has, without recognition of its anti-chronic immune-mediated disorder activity, proposed or even practiced an immunization schedule which falls within the present disclosure, If, under the applicable law, such a proposal or practice would be deemed to anticipate or render obvious an invention here claimed, then it is within the inventor's contemplation to excise from the invention the specific embodiment in question, preserving to the maximum degree permitted by law the scope of protection originally sought.

A second problem with method claim protection is that it is geared to use of immunogens to decrease the incidence or severity of a chronic immune-mediated disorder. However, the Applicant has also enriched the art by teaching it to examine the chronic immune effects of conventional immunization. A vaccine manufacturer may find, after testing inspired by Applicant, that early immunization, while less likely to elicit this adverse effect, is also less effective against the infectious disease, and therefore continue to recommend, with appropriate warnings, late immunization. A "method of reducing the incidence or severity of a chronic immune-mediated disorder" claim would not reach this practice, even though the manufacturer would clearly have benefitted from Applicants's teachings.

A third problem is that the method claims are infringed by physicians. Applicant would prefer to assert direct infringement by the manufacturer. It is easier for Applicant to monitor vaccine labeling than to identify which doctors are following the claimed early immunization strategies.

A "kit" claim, like claims 27 and 59, solve these problems, without giving Applicant control of subject matter to which he is not entitled. Claim 27 and 59 are infringed only if the immunogen is distributed or sold with labeling either giving instructions which call upon the physician to practice the invention, or warnings indicating that the manufacturer has screened the immunogen as taught by Applicant.

Claims 27 and 59 could not be inherently anticipated by the naive use of the immunogen in an early immunization schedule, since such use, by definition, would make no reference to the effect of the immunogen on the incidence or severity of a chronic immune-mediated disorder.

3.2. With regard to claim 32, this claim has been amended to avoid the possibility of inherent anticipation.

Madore

Madore's schedule is 3 doses of H. influenza B immunogen, the first at "1-2 mos", and then 2 more doses at 2 mo intervals.

While Madore's first dose of HiB is given at 1-2 months, which could be less than 42 days (assuming 2 months=60 days), the subsequent doses are given at two month intervals, and hence are both after the 42 day cutoff and at an interval greater than two weeks.

Dengrove

4 doses of DTP, the first before 4 days of age, and doses 2-4 at 2, 4 and 6 mos. Thus, only dose 1 is within the first 42 days, and the interval once again is 2 months.

John

Teaches 1st dose of oral poliovirus at 7, 14, 21, 28, 35, or 42 days; 2 more doses at 4 wk intervals.

Thus, John's earliest schedule called for immunization at 1, 5 and 9 weeks. Only two doses are in the first 42 days, and the interval is still longer than two weeks.

Halsey

1) 1 dose of oral poliovirus in first week (p. 1153, Table 1);

2) 1 dose of oral poliovirus at 1-12 weeks (p. 1154, Table 4);

3) 2-3 doses of oral poliovirus, initiated at 6-8 weeks and separated by 4-8 week intervals (p. 1155-6, Tables 3 and 4);

4) 4 doses of poliovirus, at 3, 60, 90 and 120 days (p. 1156, Fig. 2);

5) 3 doses of DPT or pertussis (p. 1160, Table 5);

6) 2-3 doses of tetanus toxoid (p. 1161, Table 6);

7) 2-3 doses of diphtheria (p. 1161, Table 7).

Halsey tabulates a large number of protocols. Those of tables 1 and 2 contemplate only a single dose. Those of Table 3 reported the effect of 2 or 3 doses, initiated at "approximately 6-8 weeks of life", and "separated by 4-8 week intervals".

In Halsey Fig. 2, a study group is said to have received poliovirus at 3, 60, 90 and 120. Only 1 dose in the first 42 days, and the interval is 30 days.

Turning to Halsey's Table 5, dealing with DPT and pertussis vaccines; the only examples allegedly featuring 3 doses before week 7 or at intervals of 2 weeks or less are Provenzano (1965) and Adams (1947). These are also the only ones with intervals smaller than 4 weeks.

Upon inspection, Halsey misquotes Provenzano (1965). While Halsey indicates that Provenzano administered at 0/1w/2w, it was actually at 0/1mo/2mo (see Provenzano, of record). The latter schedule would not anticipate.

Adams (1947) administers pertussis in three doses, at weekly intervals, within the first month. This is distinguished by limitation "(2)" of claim 32, and the "four dose" limitation of claim 56.

None of the tetanus vaccines of table 6, or the diphtheria vaccines of Table 7, satisfy the "3 in 42" or 3 at 2 week intervals or less" criteria of claims 32 and 56.

Enablement

Before analyzing the rejections in detail, we would like to lay out applicants' primary evidence of enablement/operability. The present specification presents five experimental examples, which are summarized below.

Example 1

Shows reduction in incidence of diabetes in NOD mice

receiving (a) anthrax or (b) plague, on days 8, 15 and 29. The anthrax was more potent.

Example 2

Shows further reduction in incidence of diabetes in NOD mice receiving anthrax on days 1, 3, and 10, and weeks 4, 6, 8, 10, 12 and 14. Still further reductions obtained by combining the anthrax with tetanus and diphtheria, and even more with pertussis also provided.

Also shows that first immunization of NOD mice with DTP at 8 weeks leads to higher incidence of diabetes.

Example 3

Mice were injected with cyclosporine to make them prove to developing autoimmunity, and then were immunized with (a) anthrax + diphtheria + tetanus (ADT) at days 10, 17, 31 and 45 and (b) anthrax + DTP at days 6-8, 14-16 and 27-29 (3 admin.). Both treatment groups exhibited decreased incidence of anti-(gastric antigen) autoantibodies, with the effect being greater for group (b).

Example 4

BB rats (another diabetes model) were immunized with anthrax + DTP at days 1, 4, 11, 25, 39, 53, 61, 75, 89 and 103. They showed decreased incidence of diabetes relative to control rats.

Example 5

MRL/MPJ-lpr mice were used as a model of SLE. The mice were injected with anthrax + acellular DTP at days 1, 3, and 10, and weeks 4, 6, 8, 10, 12 and 14. The incidence of glomerulonephritis (a symptom of SLE) was reduced by this immunization.

Additionally, epidemiological data is presented in Example

101 and Tables I-IV. Table I compares different countries, with different immunization plans, for the same time period (roughly 1980-1990), while the other tables look at the effect of temporal changes in immunization schemes in a single country. Table I examines the effect of pertussis and BCG immunizations in various countries; Table II shows changes in the incidence of diabetes in Finland, explained at pages 93-95 as attributable to use of Hemophilus influenza and MMR vaccines. Table III focuses on Allegheny County, Pennsylvania, and the discussion at pages 95-97 correlates changes with usage of Hemophilus influenza, pertussis and mumps vaccines. Finally, Table IV is said at pages 97-99 to evidence a connection between smallpox immunizations and diabetes. The first immunization was given earlier at the time of a smallpox epidemic.

Classen and Classen, Infect. Dis., 6:449-454 (1997) presents some additional data.

Their table 1 is new, and correlates the incidence of diabetes in Sweden with BCG and smallpox immunization practices.

Their table 2 corresponds to Table I of the application, and adds data for Sweden (1990) to group 1; Switzerland (1985-1987) to group 2; and Malta (1980-1987) to group 4. (It omitted the data for Sweden (1987) that had been given in group 4 of Table I of the application.) It also adds a group 5 ("H-influenzae, pertussis, BCG vaccination, 0-1 month and school-aged") with an entry for Finland (1988).

Their table 3 corresponds to Table II of the application, and adds 1990-1992 data for the 0-4 and 5-9 age groups.

Their table 4 is new, describing the incidence of diabetes in New Zealand, and relating it to a national hepatitis B immunization program.

Another piece of evidence is the declaration of Dr. Classen executed July 8, 1994 and filed the same day in Serial No. 08/104,529, now USP 5,728,385. Certain of the experiments which

were enumerated in this declaration are explicitly part of this CIP. Thus, section 2 of the declaration is now Example 4, section 3.1 is now Example 101, and section 4 is now Example 5. However, sections 5-8 are still worthy of study. Section 5 refers to a "table VI", attached to the declaration, and summarizing the types of vaccines affecting type I diabetes. This section addresses the issue of scope of immunogens and their mechanism of action. Section 6 relates to devising an immunization schedule; section 7, to selecting a dosage; and section 8, to immunological pathways.

1. The first issue is whether applicant is properly limited to a single combined immunogen of example 2 (anthrax + DPT).

While that was applicant's best tested immunogen, it was not the only immunogen shown to favorably affect diabetes. Anthrax alone (42.1% vs. 65% control), plague (57.9% vs. 65%), and anthrax + DT (7.7% vs. 65%) immunizations all resulted in reduced incidence, although the incidence with anthrax + DTP was 0/29 animals at 32 weeks (see Examples 1 and 2).

The effectiveness of other immunogens is also suggested by Applicant's epidemiological data (Example 101 and Classen, et al., Infect. Dis. 6:449-54 (1997)), from which Applicant reasonably inferred that early immunization with BCG and smallpox vaccines reduces the incidence of diabetes, and that late immunization with BCG, Hemophilus influenza, hepatitis B, meningococci polysaccharide, measles, mumps and rubella immunogens can increase diabetes. (The latter also implies that early immunization with the same immunogens would decrease diabetes.)

Besides the Examiner's failure to consider all examples, there are other flaws in the Examiner's reasoning that extrapolation is improper.

First of all, the agents we used (anthrax and DPT) are very different, so, if they both have this effect on autoimmune

disorders, other agents are likely to do so, too.

Secondly, we present a rational basis (lymphokine release) for expecting a general effect of this type (see pp. 15-16).

Thirdly, the unpredictability of the relationship between autoimmune disorders and microbial infections has nothing to do with our invention. We are not suppressing an autoimmune disorder by suppressing a causative infection. Our Examples show an effect in infection-free mice and rats.

These points are developed in more detail below.

The present invention is directed to methods of reducing the incidence of an autoimmune disease, by early and frequent administration of immunogens.

It can be seen from both the experimental studies and the epidemiological data that a variety of immunogens -- plague, anthrax, diphtheria, tetanus, pertussis, BCG, Hemophilus influenzae, hepatitis B and smallpox -- can affect the development of diabetes, and that early administration of BCG, plague, anthrax, anthrax + DT, anthrax + DPT, and smallpox immunogens can reduce the incidence of diabetes.[2]

Table VI of the 1994 Classen Declaration (copy enclosed), filed in the parent case, compared the anthrax, plague, DT, pertussis, Hib, BCG, smallpox and MMR vaccines in terms of the nature of the vaccine. There are considerable differences. Only the pertussis and BCG vaccines have been shown to contain an immunogen that cross-reacts to an autoantigen associated with type I diabetes mellitus.

Under these circumstances, it is clear that the anti-diabetic response cannot be entirely immunogen-specific, as there is no common epitope in question which could be eliciting the response. A nonspecific immune response must play an important

[2] The effect of early administration of the other immunogens noted is not yet known, but is readily determined.

role.

At page 15, line 14 to page 16, line 8 of the specification, Dr. Classen declares

> Without intending to be bound by any theory, early administration of immunogens can cause the release of lymphokines that may accelerate the maturation of the immune system. The immunization may act in several ways including:
>
> A. Enhancing destruction of autoimmune prone cells in the thymus;
>
> B. Enhancing the flow of normal T-cells from the thymus;
>
> C. Causing peripheral elimination of autoreactive T-cells that have escaped the thymus;
>
> D. Causing the release of interferons which prevent infection with autoimmune causing viruses; and/or
>
> E. Causing migration of macrophages into the area of administration as in an injection site and away from an vital organ like the islet cells of the pancreas. The invading macrophages have the ability to act as antigen presenting cells and induce an autoimmune response against the vital tissue.
>
> In contrast, the late administration of an immunogen can cause the release of lymphokines which may act as growth factors enabling autoimmune inducing cells to grown.

Lymphokines (and other cytokines) are discussed in more detail at pages 37-39 of the specification. Interferon alpha is specifically mentioned at page 38, line 7. The mechanism by which immunization with a broad range of vaccines at birth prevents diabetes can be explained through the release of alpha interferon (or other lymphokines). Alpha interferon is an molecule made by macrophages when they are activated by an immunological challenge such as an infectious organism or vaccine. Alpha interferon is routinely used to treat patients with hepatitis and other viral infections because the molecule

has strong and broad antiviral activity. Alpha interferon induced by immunization at birth can help prevent diabetes through the suppression of congenital or neonatal infections, also called vertical infections. Studies from Sweden and Finland have indicated that 27% or more cases of insulin dependent diabetes are linked to a vertical infection with Coxsackie B virus. See Dahlquist, et al., Diabetologia, 38:1371-3 (1995); Hyoty, et al., Diabetes, 44:652-7 (1995). This data is consistent with early reports linking the development of insulin dependent diabetes to congenital rubella infections. Ginspberg-Gellner, et al., Diabetologia, 27:87-9 (1984). Inhibition of these infections through nonspecific mechanisms, in particular release of alpha interferon following immunization at birth, explains why early immunization is associated with a reduced risk for developing diabetes. This mechanism of action also explains why early immunization prevents diabetes in NOD mice since a congenital viral infection has been suggested as a cause of diabetes in the NOD mouse. Gaskins, et al., J. Clin. Invest., 90:2220-7 (1992); Suenaga, et al., Diabetes, 37:1722-6 (1988); Nakagawa, et al., Diabetologia, 35:614-18 (1992).

The late administration of alpha interferon to patients has been reported to cause insulin dependent diabetes. Alpha interferon and the alpha interferon inducer Poly I:C have been shown to induce diabetes in rodents as well, explaining why late immunization induces diabetes in rodents. The induction of diabetes by late immunization also can be explained through the release of alpha interferon. The mechanism by which alpha interferon can induce diabetes include damaging the islet cells and speeding up a smoldering subclinical autoimmune disease.

The ability of interferon to modulate diabetes by two pathways, prevention through inhibiting viral infections and induction through stimulating an autoimmune response, explains the importance of timing of first immunization.

Potential immunogens, which could elicit, if administered early in life, an anti-diabetic immune response, are discussed in great detail at pages 33-36, 41-44, in the Examples, and original claims 3, 17 and 19.

Methods of screening immunogens for suitability are discussed at length at pages 53-75, and are further exemplified by Examples 1 to 4 of the specification.

In view of the plethora of examples of potential immunogens, the diversity of the immunogens already known to affect diabetes, the plausibility of the proposed non-immunogen-specific mechanism (lymphokine release) by which the anti-diabetic effect is exerted, and the detailed presentation of the screening methodology, it is clear that one skilled in the art can, without undue experimentation, identify additional immunogens that can, by early administration, reduce the incidence of diabetes.

Therefore it does not appear that the disclosure is enabling only for the listed immunogens, as other immunogens would be expected to have an anti-autoimmune disease effect and to be identifiable without undue experimentation.

The Examiner states that the precise relationship between auto immune responses and certain microbial infections is difficult to establish. That may be so, but the present invention does not require that one understand how the autoimmune disease is caused, merely that one interrupt the development of the autoimmune response. And even if there are "multiple mechanisms of induction of anti-self-responses", and the present invention interferes with only one of them, such interference is still an advance in the prevention of autoimmune disease.

2. The second enablement issue relates to the immunization of infants against an infectious disease (OA, page 3, line 19 to page 5, line 12; page 6, lines 11-13).

While there may be uncertainty as to the best age at which to vaccinate in order to elicit a specific, infectious disease-

protective response to the immunogen in question, that is irrelevant to devising a vaccination schedule when the purpose is just to reduce the incidence or severity of an immune disorder. Method claims 32 and 33 and kit claim '27 do not require an effect against the infectious disease. Moreover, it is irrelevant to those claims whether the immunogen derived from HCV, HIV, etc. will protect against the infectious disease in question.

Claims 31 and 36, and new claim 59 (replacing claim 25) do recite protection against an infectious disease. However, these claims contemplate use of an immunogen known to protect against the infectious disease in question, and merely call for either an immunization schedule which reduces the risk of contracting a chronic immune-mediated disorder, or (in the case of claim 59) a warning that a particular schedules could increase that risk.

The prior art taught devising an immunization schedule for immunization against infectious diseases which (1) protected against the infectious disease, while (2) keeping side effects to tolerable levels. The side effects then recognized were, for example, soreness, fatigue, and vomiting, acute allergic reactions, and contraction of the infectious disease (if not completely killed or attenuated). It was not recognized that immunization could also increase the incidence or severity of a chronic immune mediated-disorder, such as diabetes or SLE.

Based on applicants' teachings, those skilled in the art will evaluate the chronic immune adverse effects of various alternative immunization schedules, together with evaluating the acute and chronic protective immune response and the acute allergic response to the immunization.

As a result, an immunization schedule may be adopted which sacrifices some of the infection-preventive effect in return for a lower incidence or severity of chronic immune-mediated disorders, just as prior schedules have made similar compromises

to reduce other side effects.

The data shows that doses routinely given to prevent infections alter the risk of chronic immune mediated disorders. it is generally known what doses alter infections for common immunogens, e.g., pertussis, diphtheria, tetanus, polio, measles, mumps, rubella, hepatitis B, hepatitis A, hemophilus, neisseria, pneumococcus, varicella etc. The person skilled in the art only needs to determine, without undue experimentation, a dose giving an effect, not an optimal dose.

Applicant would be willing to amend claims 31, 36 and 59 to recited that the method (31) and kit (36, 59) are for "eliciting an immune response in a mammal which recognizes an immunogen associated with an infectious disease to which said mammal is susceptible", without explicitly requiring an immunizing or protective effect. See new claim 101.

3. The third issue relates to the inhibition of chronic immune mediated disorders other than diabetes. (OA, page 6, lines 2-3.)

The Examiner doubts the ability of a person of ordinary skill to adapt the teachings of the present invention to a chronic immune mediated disorder (as defined at pages 21-24 of the specification) other than diabetes.

It is well settled that the number of embodiments embraced by a claim is not the best measure of the difficulty of practicing it without undue experimentation. Disorders which are manifested through a common mechanism are likely to have a common cure or palliative. For example, a patient suffering from an allergic response may be given an antihistamine, regardless of the nature of the allergen. A particular immunosuppressant may be useful for treating a variety of autoimmune diseases.

Many patents have been issued which claim treatment of a large class of diseases while only showing examples of treating a single disease. In the field of autoimmune diseases, the

following patents come to mind:

i) U.S. patent 4,695,459 claim 3 (column 6 line 45) claims a method of treating multiple diseases in humans including multiple sclerosis, systemic lupus erythematosus, psoriasis, juvenile onset diabetes, Sjorgren's disease, thyroid disease, or myasthenia gravis. The specification only gave an example of treating EAE in mice.

ii) U.S. patent 4,710,380 claim 1 (column 5 line 47) claims a method of treating human or mammal subjects for "disorders characterized by an hyperactive immune response". The term is similar to the term chronic immune mediated disorders used in our application because both encompasses rheumatoid arthritis, lupus, type I diabetes, and other autoimmune disorders (page 36 line 8). Patent 4, 710,380 contains only examples of rheumatoid arthritis patients being treated with its claimed method, however, its claim 1 encompasses all hyperactive immune responses.

In paragraph 4 of the Classen Declaration, data is presented which shows that the method of the present invention inhibits spontaneous autoimmunity in MRL/lpr mice. These mice, absent intervention, develop a disease which closely resembles the autoimmune disorder Systemic Lupus Erythematosus (SLE) in humans. Like SLE patients, the MRL/lPr mice develop anti-DNA and anti-nuclear autoantibodies which can form immune complexes, which in turn can cause arthritis, dermatitis, and glomerulonephritis.

The MRL data is important not only because it is a good model for human SLE but because this autoimmune disease is both genetically, immunologically, and clinically very different from diabetes. Appendix 1 hereto summarizes a few references verifying both the similarity of the disease in MRL mice to SLE in humans and the clinical importance of the MRL model.

As described in the declaration, MRL/MpJ-lpr mice were injected either with a control (PBS) or with the anthrax/DTP combination, following an immunization schedule within the

teachings of the present invention. At 15 weeks, 26.3% control mice exhibited significant proteinuria (an accepted sign of glomerulonephritis), while only 7.7% of the vaccinated mice developed comparable levels of protein in their urine.

4. The fourth enablement issue is raised by the examiner's statement that the results "lend support to the early vaccination... to prevent diabetes in mice" (page 5, last two lines). To the extent that the examiner is hinting that extrapolation to other mammals, especially humans, is improper, there is not even a prima facie case, as there is no supporting reasoning or evidence. In the interest of expediting prosecution, we will nonetheless show that the law and facts support the present claims.

MPEP §2107.02(c) specifically states that "data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility". It is well settled that animal data (or even in vitro data) can establish the utility of a therapeutic method in humans if there is an accepted correlation between efficacy in the animal in question, and efficacy in humans. See In re Jolles, 206 USPQ 885 (CCPA 1980); Nelson v. Bowley, 206 USPQ 881 (CCPA 1980); Cross v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985). The law does not requires that this correlation be perfect, merely that it give the researcher a reasonable expectation that a drug which does well in animal testing will be successful in humans.

The expectation exists here because:

(1) the specification establishes efficacy in NOD mice, and NOD mice are an accepted animal model of diabetes mellitus in humans;

(2) the method of the present invention was effective in a second species of animals, BB rats, which are likewise accepted as animal models of human diabetes mellitus; and

(3) the utility of the present invention in humans is made more believable by human epidemiological data.

It is now widely accepted by those skilled in the art that type I diabetes in humans responds similarly to immune intervention as does diabetes in NOD mice and BB rats. Diabetes in all three species is considered to be an autoimmune disease based on the presence of islet cell autoantibodies and strong genetic linkage between the development of diabetes and MHC genes (New England Journal of Medicine 314:1360-1368,1986; Diabetes Reviews 1:15-42,1993). Immunological events occurring in the first 2 months of life have been clearly shown to be responsible for the development of diabetes in NOD mice and BB rats. Similarly, recent human epidemiology data shows that immunological events occurring at birth have a profound effect on the development of human diabetes. These events include maternal fetal blood group incompatibility as well as exposure to rubella virus and nitrates at birth (Diabetes Reviews 1:15-42,1993; Diabetologia 35:671-765,1992).

The concept of diabetes in humans responding similarly to diabetes in NOD mice is widely accepted. This has been justified by therapeutic experience. Clinical trials have shown that type I diabetes in humans can be prevented by immunosuppressants like cyclosporine when administered to prediabetics or newly diagnosed diabetics (Diabetes Reviews 1:15-42,1993). Immunosuppressants have a similar effect on NOD mice and BB rats (Clinical and Investigative Medicine 10:488-495,1987). The NIH recently embarked on a trial of screening up to 80,000 children to initiate a program of treating prediabetics with insulin immunotherapy, after a small phase I trial in humans supported results developed in NOD mice (Lancet 341:927-928,1993).

By reason of these findings, the art has often recognized the value of NOD mice and BB rats as models for diabetes in humans and has used these models to evaluate anti-diabetic

therapies. The citations of Appendix 2 hereto illustrate the degree of acceptance these models have earned.

As described in the attached Declaration, diabetes prone BB rats were immunized according to the method disclosed in the specification in order to show that the method of immunization could prevent diabetes in other species beside NOD mice.

BB rats spontaneously develop diabetes at an early age as is the case in NOD mice and humans. Many of the findings present in human type I diabetics and in NOD mice are found in BB rats leading experts to believe diabetes in BB rats is also a autoimmune disorder. Insulitis develops in the pancreas of BB rats before the onset of diabetes while antibodies develop to islet cells and possibly to insulin. Diabetes can be prevented by neonatal thymectomy as well as administration during the prediabetic period of cyclosporine, anti-lymphocyte antibodies, or purified lymphokines like TNF. Genetic experiments show that diabetes is closely linked to the MHC class II genes in BB rat as it is in humans. Many older rats develop autoimmune thyroiditis that is casually related to the development of diabetes as occurs in humans.

BB rats have an immunologically distinct disease from the disease in NOD mice. Diabetes develops in approximately equal numbers of males and females in contrast to NOD mice where disease develops more commonly in females. The incidence of diabetes in BB rats is not affected by gonadectomy or the administration of androgens as occurs with NOD mice. In contrast to humans and NOD mice, BB/Wor rats, the most commonly used substrain of BB rats, are severely lymphopenic. They have a marked decreased number of mature T lymphocytes in peripheral blood, spleen and lymph nodes. The CD4+ subset is substantially reduced but the CD8+ subset is almost completely absent. Natural killer cells are relatively over expressed. Several review papers have been published on this model (Diabetes and Metabolism

Reviews, 8: 9-37;1992).

BB rats were immunized with a combination of the anthrax and DTP vaccines (n=20) or nothing as a control (n=28). Groups contained approximately equal number of male and female rats. The vaccinated group was given the following dosing schedule: day 1 (.1ml,1:5); day 4 (.15ml, 1:5), day 11 (.15ml, 1:5), day 25 (.2ml, 1:5), day 39 (.2ml, 1:5), day 53 (.2ml, 1:5), day 61 (.2ml 1:2.5), and every 14 days for 3 more injections at approximately (.2ml, 1:2.5). Days of injection varied by one at times. The notation 1:5 means 1 part vaccine to 5 parts PBS. At 16 weeks of age 54% of the untreated rats had developed diabetes and or died compared to 20% in the vaccinated group. At 20 weeks of age 54% of the untreated rats had developed diabetes and or died compared to 25% in the vaccinated group. At 32 weeks the results were 54% versus 35% respectively (graph I) which represents a 34% reduction in the incidence of diabetes. The difference between the two groups were statistically significant at 20 weeks (P=0.027). The findings that the method of immunization can prevent diabetes in both NOD mice and BB rats provides strong proof that methods of immunization presented in the specification have the ability to prevent chronic immune mediated diseases in mammals with very different genetic defects.

MPEP §2107.02(d) states that "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." Nonetheless, Applicant has supplied human epidemiological data supporting his assertion of utility. This data revealed that standard childhood immunizations (i.e., later than when taught herein) against infectious disease increased the incidence of diabetes. It also indicated that early immunization with BCG and smallpox reduced the incidence of diabetes (although this effect was not recognized prior to the instant invention).

An epidemiology study described in example 101 of the

specification showed that the incidence of diabetes in western European countries was closely correlated with a country's vaccination schedule. Europe was chosen because in a relatively small geographic area there are many different countries that have different immunization schedules and the incidence of diabetes in the countries is known. The people in the western European countries have closely related racial backgrounds, diets, economic standards of living, and standards of health care. Eastern European countries of the former communist block were excluded because their standard of living and standard of medical care is not up to western levels.

The data correlating the incidence of diabetes to immunization schedule in western European countries is presented in Tables I-IV of this application.

The data in Tables I-IV discussed in Example 101, substantiates the experimental animal findings. According to Table I, administration of vaccines after 2 months increases the incidence of diabetes while administration of vaccines at birth can prevent diabetes. The findings are highly statistically significant. Administration of the pertussis vaccine after 2 month of age explains the higher incidence of diabetes in group 3 compared to most regions in group 1. Administration of the BCG vaccine after 2 months of age explains the higher incidence of diabetes in Group 4 compared to group 3. Administration of the Hemophilus influenza vaccine after 2 months of age explains the higher incidence of diabetes in group 5 compared to 4. The ability of the BCG vaccine to protect against diabetes when administered at birth explains the lower incidence of diabetes in group 2 compared to most regions in group 3.

Temporal studies (Table II-IV) were done to show the incidence of diabetes changed in a rational way after the immunization schedule changed. Published reports, showing that diabetes in humans can be caused by transient immune disturbances

at birth, are also discussed in Example 101.

The epidemiological data presented above is evidence of efficacy in humans. In re Irons, 144 USPQ 351 (CCPA 1965) held that "historical" data could be used to establish utility.

5. Finally, the Examiner refers to the alleged difficulties "calculating what dosage, method of administration, and frequency of administration" will "substantially induce an immune disorder" (see claim 2). It is, of course, as easy to determine whether an immunization schedule substantially induces a disorder as to determine whether it inhibits it. The test is the same; they are two sides of the same coin.

With regard to the issue of the determination of an effective immunization schedule, the PTO appears to have exaggerated the difficulty of this task. Applicants wish to call the Examiner's attention to the following considerations:

(a) it is routine in the art to conduct initial efficacy studies in mice and rats and to then scale-up to humans. This requires adjustment for differences in body weight, metabolism, development, etc. Such adjustments must now be deemed routine.

(b) immunization schedules are specifically suggested at pages 24-33 of the specification.

(c) dosages are discussed at pages 47-51 of the specification, and safe dosages are known for many of the contemplated immunogens.

(d) the human immunization schedules which resulted in favorable epidemiological effects on diabetes are known (see, e.g., table I, referring to vaccination with BCG at birth in 1988 in Ireland, France and Austria). Those dosages of other immunogens, such as pertussis, which, upon late administration, increased the incidence of diabetes are also known and presumably would still modulate diabetes (although more favorably) if given earlier.

The principal parameters of the immunization schedule are the timing of the first dose, the total number of doses, and the interval between doses.

The initial dosing date is addressed at page 25, lines 17-27; the total number of doses at page 25, line 28 to page 26, line 17, and the interval at page 26, line 18 to page 27, line 6. The interplay of these factors, as they affect the total number of doses within a given period, is discussed at page 27, lines 7-14.

Four specific immunization schedules are set forth in Table 5 and discussed at page 29, line 20 to page 30, line 30. These schedule can be characterized as follows:

Schedule	Initial	Total	Interval
1	w0	10	2w
2	w2	9	2w
3	w0	7	3w
4	w0	8	2wx3 3wx4

Note that schedule 4 is not entirely regular, but conforms to the practice discussed at page 26, lines 22-25.

The schedules in the Examples were

Schedule	Initial	Total	Interval
Ex. 1	8d	3	7dx1 14dx1
Ex. 2	1d	9	irregular (2d-2w)
Ex. 4	1d	10	irregular (3d-2w)

One skilled in the art would know the limitations of immunizing humans and would be able to design an vaccination schedule to perform the intended function. The frequency of immunization is limited by the frequency that individuals are willing to have a health official vaccinate their children. In Belgium in the 1960s, well baby care involved bringing the child

to the doctor every 2 weeks until the child was 8 weeks old J. Royal College of General Practitioners 24:676-686, 1974).

It is respectfully urged that with the guidance of the recommendations and examples in the specification, a person of ordinary skill in the art can develop a safe and effective immunization schedule without undue experimentation. This conclusion is confirmed by paragraph 6 of the Classen Declaration.

In general, the response is expected to be increased by administering the immunogen earlier, more often, at shorter intervals, and at higher doses. Therefore, if a preferred schedule is tried, and found less than optimal, one or more of the schedule parameters would be changed, i.e., starting earlier, giving more doses, reducing the dose interval, or increasing the size of each dose (or at least of the first dose). If the anti-diabetic response is satisfactory, but the anti-infectious disease effect (if sought), is unsatisfactory, the first dose may be given somewhat later. The practitioner may also wish to reduce the number of doses for economic reasons, or increase the time interval for the sake of patient convenience.

The systematic variation of a small number of quantifiable treatment parameters, so as to optimize the subject's response, is the very essence of routine practice.

With regard to the route of administration, several options are set forth on page 52. For each of the conventional pediatric immunogens, one or more accepted routes exist, and these would be used unless problems (not presently expected) are encountered. Most human vaccines are given intramuscularly.

Definiteness

1. In point 7, the Examiner questions the wording of the kit claims. The basic structure of the kit claims is set forth below:

> A kit...said kit comprising one or more containers each container holding...one or more immunogens, said kit further comprising labeling...

Thus, the components of the kit are clearly stated. The remaining limitations explain (a) what the labeling says, and (b) what the immunogen does. Use of functional language is permissible.

2. With regard to "total dosage... substantially greater than that required for immunization, "the Examiner asks "how much greater?" It is not necessary that all quantitative limitations of a claim be expressed as exact numbers.

The use of the relative term "substantially" has been repeatedly upheld when a suitable standard, such as a stated purpose, or representative examples, are disclosed. Andrew Corp. v. Gabriel Electronics, Inc., 6USPQ2d 2010, 2012 (Fed, Cir. 1988); Seattle Box Co., Inc. v. Industrial Crafting & Packaging, Inc., 221 USPQ 568 (Fed. Cir. 1985); In re Mattison, 184 USPQ 485 (CCPA 1975).

Here, one may compare the total dosage under a schedule intended solely to immunize against a schedule intended solely to immunize against an infectious disease with the total dosage under a preferred schedule.

Three standard schedules, reflecting prior practice, are discussed on pages 31-32. Under these schedules. during the first 112 days (16 weeks) after birth, 3 administrations are given of each immunogen. (D, T, P, polio, HepB, HiB). In the preferred schedules on pp. 107-108, schedules 3 called for five doses of HepB and six of DTP and Hib during the first 16 weeks. This clearly is considered a substantial increase in the total dosage.

3. "Pediatric" and "nonpediatric" are defined in the specification, see page 35, line 20 to page 36, line 36.

4. The functional "amount" limitation is proper and

customary in pharmaceutical method claims.

5. The "other than BCG" is proper - one can disclaim a prior art species in a genus. Applicants were concerned with the early BCG vaccinations reported by Grange and Stanford, cited at page 6, lines 11-14, and an animal study by Harada, cited on page 9, line 16 to page 10, line 4. Excission of prior art is allowed by In re Johnson, 194 USPO 187 (CCPA 1977) and here supported also by page 31, lines 9-18 and page 99, line 22 to page 100, line 2.

6. We do not see any problem with "specific times after birth". We are just saying that the doses are scheduled, not haphazard.

7. In claim 5, we have deleted one of the "BCG" entries.

Respectfully submitted,

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Enclosure
-Appendix 1
-Appendix 2
-1994 Classen Declaration
-Adams (1947)
-Classen and Classen (1997)

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Appendix 1

i. "MRL/l mice develop progressive, virulent autoimmune disease that has many of the features of systemic lupus erythematous...The MRL/l mouse model of systemic lupus erythematous provides, an experimental system that permits exploration of the effect of T-cell directed therapeutic maneuvers on the course of autoimmune disease. "(Berger, Perez, Laroche, Edelson 1990, J. Investigative Dermatology 94:52-57.)

ii. "The MRL-lpr/lpr strain of mouse spontaneously develops an autoimmune disease that closely resembles the human disease systemic lupus erythematous (SLE)." (Halpern, Hersh, Yocum 1990, Clinical Immunology and Immunopathology 55:242-254)

iii. "Murine Models of systemic lupus erythematous (SLE) have contributed significantly to our understanding of human autoimmunity. Most of the immunologic abnormalities of the human disease are also present in mouse models. One of these models, the MRL/lpr-lpr ..." (Guitierrez-ramos, Andreu, Marcos, Vegazo, and Martinez 1991, Autoimmunity 10:15-25)

iv. "Although the MRL/lpr syndrome is different from human SLE in that the lpr gene causes proliferation of an unusual subset of T-Cells, MRL/lpr disease is strikingly similar in a number of aspects to human disease." (Shlomchick, Mascelli, Shan, Radic et al. 1990; J.Exp. Medicine 171:265-297)

v."The MRL-lpr/lpr mouse, a genetic model of the human autoimmune disease systemic lupus erythematosus, has been studied extensively to determine the etiology and the pathological course of the disease in lymphoid organs" (Breneman, Moynihan, Grota, Felten, Felten 1993; Brain, Behavior, & Immunity 7:135-43)

vi."MRL/lpr and MRL/+ autoimmune mice thus provide unique models for human SLE, because they express several of the SLE-specific marker autoantibodies. These models should be useful in disclosing molecular and immunologic events governing

autoantibody expression in this condition. (Treadwell, Cohen, Williams, O'Brien, Volkman, Eisenberg 1993; Journal of Immunology 150:695-9.

vii."These results suggest a beneficial role of 1,25-D3 in the prevention or attenuation of some manifestations of murine SLE, a model sharing many immunologic features with human SLE."(Lemire, Ince, Takashima 1992, Autoimmunity 12:143-8.)

viii."The MRL-lpr murine model of systemic lupus erythematosus (SLE) has provided many insights into the pathology of human lupus."(Gallina, Steele 1991; Journal of Autoimmunity, 4:755-68)

ix."The classical types of generalized autoimmune disease in man are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Several murine strains which develop SLE and sometimes RA-like diseases are now available. They should help in the understanding of the etiopathology of SLE and RA...This paper reviews the data published about NZB, NZB/W, BXSB and MRL mice in this context." (Loor, Jachez, Montecino-Rodriguez, Klein, Kuntz, et al. 1988; International Journal of Radiation Biology & Related Studies in Physics, Chemistry & Medicine, 53:119-36.)

x." MRL/lpr mice spontaneously develop a systemic Lupus erythematosus (SLE)-like disease with a wide range of clinical and serological characteristics that mimic not only human SLE but other autoimmune disorders such as Sjogren's syndrome, and rheumatoid arthritis (RA).(Bartlett, Popovic, Raiss 1988; Scandinavian Journal of Rheumatology - Supplement. 75:290-9, 1988.)

xi."MRL-+, MRL-lpr and B6-lpr have been shown to be useful models in studying systemic lupus erythematosus."(Waterfield, Fairhurst, Chu, Levy, 1987; Immunology 61:173-8.)

Appendix 2

i) "Thus, clinical and pathological features in the NOD mouse closely resemble human type 1 (insulin dependent) diabetes mellitus." (Lampeter, Signore, Gale, and Pozzilli, Diabetologia 32:703-708, 1989; from page 703 paragraph 1 line 11)

ii) "Insulin-dependent diabetes mellitus (IDDM) is strikingly similar in the non-obese (NOD) mouse and humans" (Pacheo-Silva, Bastos, Muggia, Pankewez, Nichols, Murphy, Strom, and Rubbin-Kelley, Eur.J. Immunology 22:697-702,1992; from page 697 line 1)

iii) "Inaccessibility of the affected organ, inability to conduct prospective genetic studies, and ethical constraints on human subject research all limit the study of IDDM. For these reasons investigators have turned to animal models of the disorder. Despite the constraints of modeled systems, they have provided useful insights into the pathogenesis of the disease process. Animal models with reasonable analogy to human IDDM and a probable autoimmune pathogenesis include BB rat and the non-obese diabetic (NOD) mouse" (Rossini, Handler, Greiner, and Mordes, Autoimmunity 18:221-225,1991; from page 222 column 2 last paragraph line 4)

iv) "There is a growing interest in using NOD mice for evaluation of immune intervention protocols that might be considered in the human disease. The observation of a preventive effect of nicotinamide (see below) already has led with this substance in humans." (Kolb, Diabetes/Metabolism Reviews 3:751-758,1987; from page 765 line 34).

v) "The BB rat, NOD mouse, and other animal models have provided valuable information on the possible immunopathogenic mechanisms responsible for human IDDM". (IBID page 229 line 36)

vi) "The NOD mouse is an ideal model of organ specific autoimmune disease as well as IDDM" (Kikutani and Makino,

Advances in Immunology 51: 285-321,1992; from page 310 line 27)

vii) "The nonobese diabetic (NOD) mouse strain provides a model system for human autoimmune diabetes. This disease model is extensively used not only to examine the etiology and pathogenesis of diabetes , but also as a means to evaluate therapies." (Fox, J.Exp.Med. 175:1409-1412,1992;from page 1409, summary line 1)

viii) "The inbred nonobese diabetic (NOD) mouse spontaneously develops an autoimmune diabetes, which is now recognized as an experimental model for human insulin-dependent diabetes mellitus." (Fitzpatrick, Lepault, Homo-Delarche, Bach, and Dardene, Endocrinology 129:1382-1390, 1991; page 1382 column 1 line 1.)

ix) "The nonobese diabetic (NOD) mouse strain described originally by Maiko et al. develops diabetes spontaneously and is considered a good model for autoimmune insulin-dependent diabetes mellitus." (Hawkins, Gala, and Dunbar P.S.E.B.M. 02:201-205,1993; from page 201 column 1 line 1)

x) "Nonobese diabetic (NOD) mice spontaneously develop diabetes remarkably similar to human autoimmune insulin dependent diabetes mellitus" (Jacob, Aiso, Michie, Mcdevitt,and Acha-Obea; Proc. National Acad.Sci.USA 87:968-972, 1990; page 968 column 1 first line first paragraph)

xi) "The nonobese diabetic mouse (NOD) is considered to be an animal model suitable for studying the pathogenesis of human autoimmune insulin-dependent diabetes mellitus" (McInerney, Pek and Thomas, Diabetes 40:715-725,1991; Page 715 column 2 line 1)

xii) "The nonobese diabetic (NOD) mouse, an animal model of spontaneous diabetes, shares many features with human insulin-dependent diabetes mellitus (IDDM), including the abrupt onset of overt diabetes, the dependance of exogenous insulin to sustain life, the presence of lymphocytic infiltration of islet cells before the onset of hyperglycemia, and prevention of disease by

immunotherapy" (Karounos and Thomas, Diabetes 39:1085-1090,1990; page 1085 column 1 first paragraph line 1).

xiii) "The spontaneously diabetic BB rat is an excellent laboratory 'model' of type I (insulin dependent juvenile onset) diabetes mellitus, with both metabolic and immunological defects." (Yale and Marliss, Cln.Exp.Immunol 57:1-11,1984; page 1 introduction line 1)

xiv) "The availability of two excellent animal models for type I diabetes mellitus promises to lead to a better understanding of genetic mechanisms which can cause the autoimmune destruction of the beta cells in the pancreatic islets of Langerhans. In the nonobese diabetic (NOD) mouse,..." (Kastern, Lang and Sorensen, Current Topics in Microbiology and Immunology 156:87-102, 1990; page 87 paragraph 2 line 1)

xv) "Insulin-dependent diabetes mellitus (IDDM) is an organ-specific autoimmune disease. The NOD mouse is an excellent animal model of human IDDM." (Wang, Singh, Warnok, and Rajotte, Diabetes 41:114-117,1992; page 114 column 2 line 1) xvi) "Type I diabetes is known to occur in three different species: man, nonobese diabetic (NOD) mouse and Bio Breeding (BB) rat." (Dotta and Eisenbarth, Clinical Immunology and Immunopathology 50:S85-S95,1989; Page S86 paragraph 2 line 1).

xvii) "Insulin-dependent diabetes (IDDM) of both humans and NOD strain mice becomes clinically overt after most of the beta cells in the islets have been destroyed by an autoimmune process." (Elias, Reshef, Birk, van der Zee, Walker, Cohen, Proc. Natl. Acad. Sci. 88:3088-3091, 1991; page 3088 column 1 paragraph 1).

xviii) "One may reasonably ask if data obtained in rat models apply to humans. The answer is a qualified yes. For example, human clinical trials using cyclosporin were begun after successful use in the BB rat." (Rossini, Mordes, and Like, Ann Rev. Immunolog. 3:289-320,1985; from page 310 line 33).